Table 43: Incidence of serious complications during chronic phase of FRISC and FRIC trials by treatment

Type of Disorder	Preferred Term	Placebo N = 1180		Fragmin N = 1185	
		n	%	n	%
Body as a whole – general	Asthenia	0	0.0	1	0.1
	Back pain	0	0.0	1	0.1
	Fever	0	0.0	1	0.1
Cardiovascular – general	Aneurysm	2	0.2	0	0.0
	Cardiac failure	2	0.2	1	0.1
	Hypotension	1	0.1	0	0.0
	Hypotension postural	0	0.0	1	0.1
Central and peripheral nervous system	Convulsions	0	0.0	1	0.1
	Vertigo	0	0.0	1	0.1
Gastrointestinal system	Abdominal pain	0	0.0	1	0.1
	Gastritis	0	0.0	2	0.2
	Nausea	0	0.0	1	0.1
	Vomiting	0	0.0	1	0.1
Heart rate and rhythm	Fibrillation atrial	1	0.1	2	0.2
	Fibrillation ventricular	1	0.1	1	0.1
Metabolic and nutritional	Diabetes mellitus	0	0.0	1	0.1
	Gout	1	0.1	0	0.0
	Hyperglycemia	0	0.0	1	0.1
	Hypoglycemia	1	0.1	0	0.0
Musculoskeletal system	Accident	0	0.0	1	0.1
Myo-, endo-, pericardial and valve	Endocarditis	0	0.0	1	0.1
Platelet, bleeding, and clotting	Embolism pulmonary	1	0.1	2	0.2
	Thromboembolism	0	0.0	1	0.1
Psychiatric	Depression	1	0.1	0	0.0
Red blood cell	Anemia	0	0.0	1	0.1
Respiratory system	Asthma	0	0.0	1	0.1
	Pneumonia	1	0.1	3	0.3
	Pulmonary edema	3	0.3	1	0.1
Skin and appendages	Skin disorder	1	0.1	0	0.0
Vascular (extracardiac)	Cerebrovascular disorder	4	0.3	3	0.3
Vision	Retinal detachment	0	0.0	1	0.1

Source: Safety Table 15d

* Serious adverse events other than major bleeding, minor bleeding, thrombocytopenia, and allergic reaction

Sponsor's Table, Page 8/30/71

4.3.2 Types of adverse events resulting in treatment discontinuation during the acute treatment phase

Treatment with study medication was discontinued in 95 patients due to adverse events during the acute phase: Fragmin 3.7%, heparin 3.7%, and placebo 1.6%(Table 44).

Table 44: Types of adverse events resulting in treatment discontinuation during the acute treatment phase

Type of Event	Placebo N = 760*		Fragmin N = 1497†		Heparin N = 731‡	
	n	%	n	%	n	%
Bleeding (major or minor)	3	0.4	30§	2.0	15	2.1
Thrombocytopenia	1	0.1	1	0.1	2	0.3
Allergic reaction	0	0.0	2	0.1	1	0.1
Other complications	5	0.7	15	1.0	10	1.4
Laboratory changes¶	9	1.2	12	1.6	NA	NA
Overall incidence	12	1.6	56	3.7	27	3.7

Source: Safety Table 16a

* No information available: thrombocytopenia = 5 patients

† No information available: bleeding events = 7 patients; thrombocytopenia = 16 patients; allergic reaction = 4 patients

‡ No information available: bleeding events = 2 patients; thrombocytopenia = 4 patients; allergic reaction = 1 patient

§ This number does not include one patient who withdrew from treatment at his own request due to bruising on the stomach (patient 8005 from the FRIC trial)

¶ This category applies to the FRISC trial only. For the FRIC trial, withdrawals due to changes in laboratory values are included with other complications.

Abbreviation: NA = not applicable

Note: Patients may be included in more than one type of event.

Sponsor's Table, Page 8/30/63

4.3.3 Types of adverse events resulting in treatment discontinuation during the chronic phase

Treatment with study medication was discontinued for 57 patients due to adverse events during the chronic treatment phase: Fragmin 2.7%, placebo 2.1% (Table 45)

Table 45: Types of adverse events resulting in treatment discontinuation during the chronic phase

	Placebo N = 1180*		Fragmin N = 1165†	
Type of Event	n	%	n	%
Bleeding (major or minor)	4	0.3	9‡	0.8
Thrombocytopenia	0	0.0	0	0.0
Allergic reaction	2	0.2	4	0.3
Other complications	19	1.6	17	1.4
Laboratory changes§	1	0.2	3	0.5
Overall incidence	25	2.1	32	2.7

Source: Safety Table 16c

* No information available: bleeding events = 23 patients; *thrombocytopenia* = 10 patients; allergic reaction = 4 patients

† No information available: bleeding events = 17 patients; thrombocytopenia = 10 patients; allergic reaction = 5 patients

‡ *This number* does not include patient 16012 (FRISC), 17054 (FRISC), or 1070 (FRIC). These patients experienced injection site bruising, *GI hemorrhage*, or epistaxis, respectively. Detailed information can be found in supplemental information to Safety Tables 16 and 17.

§ *This category* applies to the FRISC trial only. For the FRIC trial, withdrawals due to changes in laboratory values are included with other complications.

Note: Patients may be included in more than one type of event.

Sponsor's Table, Page 8/30/64

4.4 Laboratory evaluations

4.4.1 Hemoglobin

Group mean hemoglobin values at baseline were similar between treatment groups within gender (Table 46).

All groups, including placebo, showed a decrease in mean hemoglobin during the study.

Table 46: Hemoglobin (g/L): mean and standard deviation over time by treatment and sex

	Placebo		Fragmin (FRISC)		Fragmin (FRIC)		Heparin	
Males	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**
Baseline	492	145 ± 13	471	145 ± 12	468	146 ± 12	480	146 ± 13
Day 1 to 3*	476	144 ± 13	450	144 ± 13	423	140 ± 13	417	139 ± 15
Day 5 to 8†	451	142 ± 13	443	140 ± 12	375	140 ± 13	369	140 ± 14
Females	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**
Baseline	268	135 ± 11	275	136 ± 11	281	135 ± 12	250	135 ± 13
Day 1 to 3*	258	133 ± 11	264	134 ± 12	261	129 ± 13	223	128 ± 12
Day 5 to 8†	239	129 ± 11	253	130 ± 11	234	127 ± 13	192	128 ± 13

Source: FRISC [1], FRIC [2]
* Data collected between days 1 and 3.
† Data collected between days 5 and 8.

Sponsor's Table, Page 8/30/72

Seven patients had recorded hemoglobin values less than 80 g/L after treatment with study drug (Fragmin 2, heparin 1, placebo 4) (Table 47)

Table 47: Hemoglobin values of less than 80 g/L after treatment with study medication

Patient	Treatment	Baseline value (g/L)	Low value (g/L)	Day of low value	Last day of treatment
17052	Fragmin	143	76	34	33
4015	Heparin	72	63, 69	2, 6	6
8103	Fragmin	122	71	5	3
11035	Placebo	115	74	173	16
12086	Placebo	144	62	164	1
21082	Placebo	135	77	33	25
26017	Placebo	162	64	121	46

Source: Lists IX A b, IX B

Sponsor's Table, Page 8/30/73

4.4.2 Platelets

The mean platelet count was similar in each treatment group at baseline and during the acute treatment phase (Table 48).

Table 48: Platelets (x10⁹/L) mean and standard deviation over time by treatment

	Placebo		Fragmin (FRISC)		Fragmin (FRIC)		Heparin	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Baseline	758	232 ± 58	739	236 ± 67	746	230 ± 64	728	230 ± 62
Day 1 to 3*	721	228 ± 54	712	228 ± 65	677	218 ± 57	638	218 ± 59
Day 5 to 8†	681	241 ± 60	691	237 ± 66	600	222 ± 60	556	223 ± 61

Source: FRISC [1], FRIC [2]
* Data collected between days 1 and 3.
† Data collected between days 5 and 8.
Abbreviation: SD = standard deviation

Sponsor's Table, Page 8/30/73

4.5 Summary of Safety events

The FRISC study showed significantly more minor bleeding in the patients treated with either 150 or 120 IU/kg of Fragmin during the acute phase as compared with placebo. Increased minor bleeding was also seen in the chronic phase at the 120 IU/kg dose as compared with placebo (See Table 15 and Table 14).

The FRIC study showed significantly more minor bleeding in the Fragmin group than in the placebo group during the chronic phase (See Table 31).

5. OVERVIEW OF EFFICACY (FRISC and FRIC combined

5.1 Comparison of FRIC and FRISC

5.1.1 Primary endpoints

FRISC looked at the incidence of death and/or myocardial infarction, while FRIC added recurrence of angina and looked at the composite of death, myocardial infarction, and/or recurrent angina.

FRISC looked at the acute phase of treatment (Day 1-6), while FRIC looked at the extended phase of treatment (Day 6-45).

5.1.2 Treatment sequence

FRISC patents received Fragmin or placebo throughout both phases of treatment. FRIC patients received Fragmin or heparin followed by Fragmin or placebo (See Appendix 0)

5.1.3 Aspirin

FRISC used 75 mg/day after a "bolus" of 300 m.g. (in patients who were not already on aspirin) and FRIC used 100-165 m.g. /day.

5.1.4 Age range

The FRISC study limited enrollment to patients over the age of 40. The ages ranged from 40-92 years of age.

The FRIC study did not limit the age, and had a range of 25-92 years of age.

5.2 Efficacy results

5.2.1 FRISC

The sponsor showed that Fragmin reduced the primary endpoint (rate of death and/or MI) from 4.8% to 1.8% with a p value of 0.001 during the first 6 days of treatment.

This effect, however, was no longer present at 45 days, or at three months. Although there was a numeric advantage seen in the Fragmin group, it was not statistically significant.

Other, secondary, objectives were also achieved. During the acute phase, the Fragmin-treated patients had a decreased need for heparin and nitroglycerin infusion as compared with placebo.

There was an indication that, at 45 days, the Fragmin group had lower incidence of MI, need for heparin, and need for nitroglycerin infusion and revascularization.

5.2.2 FRIC

In phase II, the sponsor was unable to show that Fragmin reduced the primary endpoint (death, myocardial infarction and/or recurrence of angina between day 6-45) compared to placebo.

In phase I, the Fragmin patients had a higher incidence of death, myocardial infarction and/or recurrence of angina, but the difference was not statistically significant.

6. DEFINITION OF UNSTABLE ANGINA

6.1.1 Use of the term unstable angina on the label

In the labeling section (page 2/1/5) the sponsor states that

> "Fragmin @ injection is indicated for the treatment of unstable angina and non-Q-wave myocardial infarction for the prevention of ischemic complications in patients on concomitant aspirin therapy"

6.1.2 Sponsor's definition of unstable angina in the protocol

The sponsors definition of unstable angina in the protocol:

Fulfill at least one of the following history criteria:

- Newly developed angina pectoris during the previous two months.
- Increased angina pectoris during the previous two months.
- Ongoing chest pain, with a suspicion of myocardial infarction.

Fulfill at least one of the following ECG criteria without any explanation other than myocardial ischemia:

- Temporary or manifest ST-depression with at least 0.1 mV (> 1 mm) in at least 2 adjacent leads (irrespective of T-wave changes).
- Temporary or manifest T-inversion with at least 0.1 mV (> 1 mm) below the baseline in at lest 2 adjacent leads (without pathological Q-waves in the same leads).

6.1.3 Braunwald's classification of unstable angina

This is the classification of unstable angina, which, in modified form, is used in the studies to define unstable angina.[9]

Class I: New onset severe or accelerated angina. Patients with new onset (<2 months in duration) exertional angina pectoris that is severe or frequent (≥ 3 episodes/day) or patients with chronic stable angina who develop accelerated angina (that is, angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding 2 months.

Class II: Angina at rest, subacute. Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.

Class III. Angina at rest, acute. Patients with one or more episodes of angina at rest within the preceding 48 hours.

Braunwald also discusses organizing unstable angina by Class A, B, and C, based on whether the angina can be related to a non cardiac cause and whether the angina is occurring in the peri infarct period.

Electrocardiographic changes are not required in Braunwald's system. If electrocardiographic changes are present, they are simply noted.

It is also of note that new onset of angina (< 2 months) is not considered unstable unless it is severe, or frequent, or crescendo.

A summary of Braunwald's system is in Table 49.

Table 49: Braunwald's classification system for unstable angina [9]

Severity	Clinical circumstances		
	A. Develops in presence of extracardiac condition that intensifies myocardial ischemia (secondary UA)	B. Develops in absence of extracardiac condition (primary UA)	C. Develops within 2 wk after AMI (postinfarction UA)
I. New onset of severe angina or accelerated angina; no rest pain	IA	IB	IC
II. Angina at rest within past month but not within preceding 48 hr (Angina at rest, subacute)	IIA	IIB	IIC
III. Angina at rest within 48 hr (Angina at rest, acute)	IIIA	IIIB	IIIC

Patients with UA may also be divided into three groups depending on whether UA occurs 1) in the absence of treatment for chronic stable angina, 2) during treatment for chronic stable angina, or 3) despite maximal anti-ischemic drug therapy. These three groups may be designated by subscripts 1, 2, or 3, respectively.
Patients with UA may be further divided into those with and without transient ST-T wave changes during pain.
UA, unstable angina; AMI, acute myocardial infarction.

6.1.4 Definition of unstable angina in common use

Taken from Harrison's *Principles of Internal Medicine*[10]:

> "The following three patient groups may be said to have unstable angina pectoris: (1) patients with new onset (<2 months) angina that is severe and/or frequent (≥3 episodes per day); (2) patients with accelerating angina, i.e., those with chronic stable angina who develop angina that is distinctly more frequent, severe, prolonged, or precipitated by less exertion than previously; (3) those with angina at rest."

Again, electrocardiographic changes are not required and new onset (< 2 months) angina is not considered unstable unless it is severe.

6.1.5 Conclusion

These studies have excluded all patients with unstable angina who did not have EKG changes.

Labeling, if Fragmin becomes approvable for this indication, should make it clear that Fragmin has been studied in a sub-set of patients with unstable angina, i.e. those with electrocardiographic changes.

7. LABELING REVIEW

7.1 Proposed Labeling

The sponsor is proposing the following label additions:

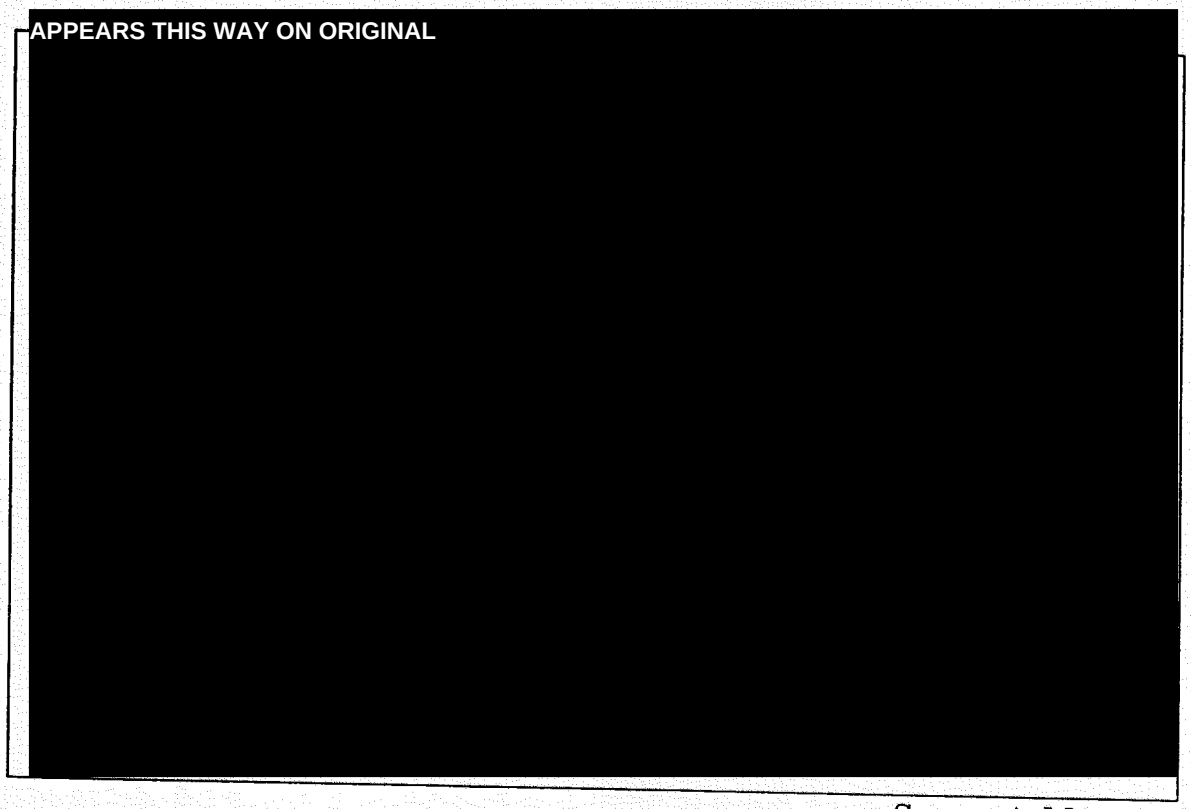
DRAFT LABELING

[redacted]

DRAFT LABELING

[redacted]

APPEARS THIS WAY ON ORIGINAL



Sponsor's Material

7.2 Review of labeling

See the CSO's review.

8. CONCLUSION

8.1 Efficacy

The FRIC study does not support this application. FRIC did not achieve its primary endpoint, which was to show that Fragmin reduced the incidence of death, myocardial infarction and/or recurrent angina after prolonged treatment. Nor did it achieve any other endpoints.

The sponsor concludes that FRIC showed that heparin was "comparable" to Fragmin during Phase I (day 0-6). This is essentially an equivalence or non inferiority claim. FRIC was not powered to support anything but a superiority claim. It is not possible to conclude anything about the equivalence of these two treatments.

Furthermore, the Fragmin patients had a higher, albeit not statistically significant, incidence of the triple endpoint of death, myocardial infarction and/or myocardial infarction.

The FRISC study achieves its primary endpoint and provides strong evidence that Fragmin is effective in the treatment of patients with unstable coronary artery syndromes during the acute phase (0-6 days) of the study as measured by the primary combined endpoint of death and/or myocardial infarction.

This effect is not maintained at a statistically-significant level during the chronic phase of the study. At day 40, there was not a statistically-significant difference in death and/or M.I. as determined by the Cochran-Mantel-Haentzel test. A logrank analysis of the cumulative probability of death and/or M.I. through day 40 did show a statistically-significant difference. However, this analysis did not include four patients who had silent M.I.'s.

Other secondary endpoints are also achieved at day 40. These included need for i.v. heparin, need for i.v. nitroglycerine, revascularization, and various combinations of these secondary endpoints.

A double endpoint of death and/or myocardial infarction is a significantly more robust endpoint than triple endpoints (with the addition of revascularization of refractory angina) other sponsor's have used to support the same indication.

Given the robustness of the FRISC endpoint, the high degree of statistical significance with which it was achieved, the fact that multiple other related endpoints were also achieved at a highly statistically-significant level, and the fact the trend was still seen at day 40, the FRISC study is adequate to stand on its own as a single study to support the current indication.

8.2 Safety

Serious bleeding and other adverse events were similar in the Fragmin and heparin/placebo groups. However, there was a statistically significant increase in minor bleeding in the Fragmin groups compared to either placebo or heparin.

9. RECOMMENDATIONS

9.1 Approvable

Fragmin,® at 120 IU/kg (Max 10,000 IU/dose) s.c. every 12 hours, is approvable, for the treatment of patients with unstable angina (with EKG changes) or non-Q-wave M.I., for six days, to prevent death and/or Q-wave M.I..

/S/ [redacted]

John W. Schmeling, M.D., Ph.D.

cc:
NDA 20-287/S-10
HFD-180
HFD-180/LTalarico /S/ 5-25-99
HFD-180/KRobie-Suh
HFD-180/JSchmeling
HFD-181/KOliver
HFD-180/JChoudary
HFD-180/EDuffy
f/t 5/24/99 jgw
N/20287905.JWS

10. APPENDICES

10.1 Definition of Unstable Coronary artery disease (FRISC)

FRISC (pages 8/1/61 and 8/1/62)

"Patients with modified Braunwald I, II, or II classification (with the addition of ECG changes) or patients with non Q-wave MI (ECG changes and elevated enzymes) were defined as unstable coronary artery disease in this trial."

Class I. Patients with first appearance of rest angina >2 months ago or no rest angina.

Class II. Patients with rest angina starting between 48 hrs and 2 months ago.

Class III. Patients with rest angina starting < 48 hours ago

10.2 Definition of myocardial infarction (FRISC 8/3/54-56)

Acute Myocardial Infarction - diagnosis and definitions

Definite myocardial infarction

* Evolving diagnostic ECG or two of the following categories:
  1. Prolonged cardiac pain
  2. Isolated diagnotic ECG
  3. Abnormal enzymes

* Q-wave infarction: Definite MI including an abnormal Q-wave

* Non-Q-wave infarction: Definite MI without the development of an abnormal Q wave.

Possible Myocardial Infarction

1. Prolonged cardiac pain + equivocal ECG
2. Prolonged cardiac pain + equivocal enzymes
3. Isolated diagnostic ECG + equivocal enzymes
4. Equivocal ECG + equivocal enzymes
5. Abnormal enzymes alone

Prolonged cardiac pain

* Pain occurring anywhere in the anterior chest, left arm or jaw, which may also involve the back, shoulder, right arm or abdomen on one or both sides.
* for more than 20 minutes

ECG (12-leads)

* Evolving diagnostic ECG:
  Two or more ECG recordings during the hospitalization showing the appearance of a new Q-wave or the disappearance of an R-wave or an ST-T segment elevation followed by an T-wave inversion in at least two leads.

* Isolated diagnotic ECG:
  An abnormal Q-wave or/ST-T segment elevation plus a T-wave inversion in at least 2 leads.